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# Chemoprevention: Drugs that can reduce breast cancer risk

If you're at high risk of breast cancer, you may wonder what you can do to lower your risk. Besides adopting a healthy lifestyle, your doctor may recommend taking certain medicines (chemoprevention) to reduce your cancer risk.

Chemoprevention isn't for everyone, though. Weigh the pros and cons before giving your approval. Ask your doctor about the benefits, risks and side effects associated with each drug used.

Your conversation with your doctor should be ongoing, mirroring the ongoing study of different drugs designed to reduce cancer risk. For instance, the latest results from the Study of Tamoxifen and Raloxifene (STAR) trial show that raloxifene works as well as tamoxifen for breast cancer prevention. But each drug is associated with distinct quality of life issues.

## What places you at high risk of breast cancer?

You're considered at high risk of breast cancer if:

- You have a strong family history of breast cancer
- You have a mutation in one of the breast cancer (BRCA) genes
- You've had a breast biopsy revealing abnormal cells (atypical hyperplasia) in a duct or lobule of your breast
- You've had lobular carcinoma in situ (LCIS)

To assess your risk of breast cancer, your doctor might calculate your Gail model score. The Gail model takes into account certain risk factors and gives you a score for your five-year risk and your lifetime risk of developing breast cancer. A five-year risk estimate of 1.66 percent or greater indicates an increased risk of breast cancer. This score — 1.66 percent — means your chances are 16 to 17 in 1,000 of developing breast cancer over the next five years.

## Which drugs are used in chemoprevention?

Only one drug — tamoxifen (Nolvadex) — has been officially approved by the Food and Drug Administration (FDA) to help protect high-risk women from getting breast cancer. Tamoxifen is approved for use among women age 35 and older who have a five-year Gail model score of 1.66 percent or greater. It's generally taken for five years. Research is underway to determine if other drugs can do the job, too. These drugs include raloxifene (Evista), aromatase inhibitors and nonsteroidal anti-inflammatory drugs.

These drugs work through different mechanisms. Some of the drugs block the action of estrogen, and others reduce the amount of estrogen your body makes. Although estrogen is the primary female hormone, affecting many areas of health, it also influences the growth and development of certain breast tumors.

## Selective estrogen receptor modulators

Tamoxifen and raloxifene aren't hormones. They belong to a class of drugs called selective estrogen receptor modulators (SERMs). These drugs bind to the same protein that the hormone estrogen needs to exert its effects.

But whereas estrogen can promote the growth of breast cancer cells, SERMs can either have the same effect or block the estrogen from fueling abnormal growth. Which they choose to do depends on which tissue is involved as well as the individual SERM. This explains why your doctor might choose one SERM over another or none at all.

**Tamoxifen**
Tamoxifen is a SERM that blocks estrogen's ability to stimulate breast tumor growth. It also has estrogen-like effects on the uterine lining. Tamoxifen is used to treat advanced cancer and, for women whose cancer is early-stage estrogen receptor positive, it's used to keep the cancer from coming back after treatment.

Tamoxifen is also prescribed for women who haven't been diagnosed with breast cancer but who are at high risk of the disease. A review of the data from several clinical prevention trials — studies conducted in North America, England and Europe — found that tamoxifen use results in a 38 percent reduction in risk of both invasive and noninvasive breast cancer.

Tamoxifen does carry the risk of side effects:

- Hot flashes
- Vaginal discharge
- Vaginal dryness or skin irritation
- Menstrual irregularities
- Headaches
- Nausea

Although uncommon, it can also cause potentially life-threatening blood clots, endometrial cancer or uterine tumors (uterine sarcoma).

Whether you take tamoxifen will depend on your age, risk status, family history, medical history, lifestyle and personal preferences.

In general, tamoxifen provides the greatest benefit with the fewest side effects if:

- You're at high risk of developing breast cancer. For instance, you have a personal or family history of breast cancer or precancerous changes such as atypical hyperplasia or lobular carcinoma in situ (LCIS)
- You're premenopausal and you aren't at risk of developing blood clots or uterine cancer
- You've had a hysterectomy

If you're considering tamoxifen to reduce your risk of breast cancer, weigh the potential benefits and risks in light of your individual risk profile. As a preventive measure, taking tamoxifen doesn't guarantee that you'll remain cancer-free. Unless you're at high risk of developing breast cancer, the potential risks of tamoxifen may outweigh the benefits.

**Raloxifene**

Raloxifene, another SERM, is approved by the FDA for use only in postmenopausal women to prevent and treat osteoporosis. But researchers are investigating whether raloxifene may also reduce the risk of breast cancer. Like tamoxifen, raloxifene binds to estrogen receptors in breast tissue and blocks estrogen's effects in the breasts. Unlike tamoxifen, raloxifene doesn't have estrogen-like effects on the uterus.

In a large clinical trial — the Multiple Outcomes of Raloxifene Evaluation (MORE) trial — designed to study the effects of raloxifene on osteoporosis, investigators noted that raloxifene reduced the risk of estrogen receptor positive breast cancer by 84 percent, when compared with placebo. Raloxifene didn't affect cancers that were estrogen receptor negative. Of note, however, this trial focused on older, postmenopausal women with osteoporosis, not on younger women at increased risk of breast cancer.

To learn more about raloxifene and breast cancer prevention, the National Cancer Institute launched the STAR trial in 1999. This study compared raloxifene with tamoxifen in reducing breast cancer development in high-risk, postmenopausal women who had never before been diagnosed with the disease. Initial results from this trial show that raloxifene is as effective as tamoxifen in reducing breast cancer risk — with fewer side effects. Both drugs reduced breast cancer risk by about half.

Like tamoxifen, raloxifene may cause side effects, including hot flashes, vaginal dryness or vaginal irritation. It's also associated with an increased risk of developing blood clots. Women in the STAR trial taking raloxifene experienced 29 percent fewer blood clots and 36 percent fewer uterine cancers — a known serious side effect of tamoxifen — than did women in the tamoxifen group.

STAR trial researchers noted important differences between the two drugs in certain quality of life measures. The women in the study who took tamoxifen reported better sexual function, but they also had more hot flashes, bladder problems, leg cramps and gynecologic problems, such as vaginal discharge. Women taking raloxifene, on the other hand, experienced more frequent bone and muscle problems, pain during intercourse and weight gain.

If the FDA decides to approve raloxifene for breast cancer risk reduction, postmenopausal women may have a choice between taking tamoxifen and raloxifene in the future. However, even if you're at increased risk of breast cancer, taking tamoxifen or raloxifene to reduce your breast cancer risk might not be the best option for you.

As with any breast cancer prevention strategy, whether or not to proceed with a certain intervention is a highly individualized choice. Keep things such as possible side effects and quality of life issues in mind as you consider your options. Talk with your doctor to weigh the pros and cons in light of your own personal circumstances.

## Aromatase inhibitors

Aromatase inhibitors reduce estrogen levels in a woman's body by preventing an enzyme called aromatase from converting other hormones to estrogen. By reducing the amount of estrogen in your body, you deprive breast cancer tumors of the fuel they need to grow and thrive.

Three aromatase inhibitors are currently used to treat breast cancer in postmenopausal women:

- Anastrozole (Arimidex)
- Exemestane (Aromasin)
- Letrozole (Femara)

One large clinical study, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, evaluated anastrozole as an additional (adjuvant) treatment for breast cancer. The study found that anastrozole was slightly better than tamoxifen in reducing the risk of breast cancer recurrence in women who had estrogen receptor positive tumors. The ATAC trial also found that anastrozole reduced the risk of developing a new cancer in the other breast by 58 percent.

These promising results have led researchers to embark on a number of studies to evaluate the effectiveness of aromatase inhibitors in preventing breast cancer in high risk women who haven't been diagnosed with breast cancer.

Aromatase inhibitors appear to be at least as effective as and possibly better than tamoxifen, with fewer side effects. Serious adverse effects, such as blood clots and uterine cancer, are less common with aromatase inhibitors. Some aromatase inhibitors

may contribute to bone loss, but the extent of this potential side effect hasn't been fully determined.

## Nonsteroidal anti-inflammatory drugs

Several studies have tried to determine if aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) affect breast cancer risk. NSAIDs include many common over-the-counter painkillers, such as ibuprofen (Advil, Motrin, others) and naproxen sodium (Aleve).

Some research has found that women who had breast cancer and who regularly take aspirin or other NSAIDs have a slightly decreased risk of breast cancer recurrence. But other studies haven't shown a significant association between breast cancer risk and NSAIDs.

An analysis of data from the Women's Health Initiative study found that postmenopausal women who took two or more NSAID tablets — aspirin, ibuprofen or related drugs — a week for five to nine years cut their risk of breast cancer by 21 percent. Regular use for 10 years or more was associated with a 28 percent reduction in risk. In that study, use of ibuprofen was associated with greater protection. Other studies have found greater risk reduction with aspirin.

The benefits of NSAIDs in lowering breast cancer risk were seen only in standard doses, not in low doses such as those found in baby aspirin. Benefits weren't associated with acetaminophen (Tylenol), which relieves pain through other mechanisms.

It remains unknown how exactly aspirin and other NSAIDs help protect against breast cancer. Researchers speculate that the medications work by blocking the activity of cyclooxygenase (COX) enzymes, which may reduce estrogen levels and prevent tumors from forming. However, some NSAIDs, such as celecoxib (Celebrex) and naproxen sodium (Aleve), may increase your risk of heart attack and stroke. It's wise to discuss your individual risk profile with your doctor to determine whether the potential benefits of taking an NSAID outweighs the risks for you.

Educate yourself on your options, weigh the pros and cons of the chemopreventive medicines and consult with your doctor before making your decision about chemoprevention and whether it's the right choice for you.

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By Mayo Clinic Staff
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